REMARKS

Claims 88-107 are currently pending. New claims 88-111 have been added. Applicant note that previously presented claims have been cancelled and new claims have been added for ease of consideration. Claims 88, 89 and 98 correspond to previously presented claims 75, 76 and 87, respectively. These claims are supported by the specification at, for example, pages 2, 6-7, 9-10 and 30-31. Support for claims 90-97 and 99-111 can be found in the specification at, for example, pages 3, 11-12 and 30-31. New claims 88-111 do not constitute new matter.

The Examiner has rejected claims 75, 76, 78, 79, and 83-87 under 35 U.S.C. § 103(a) as obvious over Andersen *et al.* (U.S. Patent No. 5,955,077) ("Andersen"). For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

The Claims Are Not Obvious

The Examiner has rejected claims 75, 76, 68, 79, and 83-87 under 35 U.S.C. § 103(a) as obvious over Andersen *et al.* (U.S. Patent No. 5,955,077) ("Andersen"). The Examiner states that:

> Andersen et al teaches the polypeptide ESAT-6 as well as the amino acid sequence (SEQ ID NO:2). The peptides (SEQ ID NO: 1-11) claimed by Applicants are set forth in disclosed SEQ ID NO:2.... The prior art of Andersen et al does not specifically teach the individually claimed peptides as set forth in SEQ ID NO: 1-11. However, Andersen et al teaches that ESAT-6 is a protein that has been identified as one useful in the diagnosis of tuberculosis and that subsequences of the protein can be used so long as it has the same immunological characteristics and that subsequences of the ESAT-6 can be used in diagnostic methods.... It would have been [obvious] to a person of ordinary skill in the art at the time the invention was made to... [determine] segments of the ESAT-6 protein that function in the same manner as the complete ESAT-6 protein and use them for diagnostic purposes.

The Examiner notes that the claims do not set forth that the claimed method is an improvement over known methods of tuberculosis diagnosis, and that the specific advantageous improvements over previous methods have not been adequately outlined to show that the claimed methods are more sensitive. The Examiner states that because the advantages of the presently claimed methods are not set forth in the claims, they do not overcome the previous obviousness rejections because any limitations found in the specification are not read into the claims.

In response, and without conceding the correctness of the Examiner's position, but only to advance prosecution of the application without harming claim scope, Applicants have amended the claims. Indeed, Applicants submit that the Examiner has not set forth a *prima facie* case of obviousness, and submit that the scope and contents of the art cited by the Examiner do not encompass scope and contents of the present invention. See MPEP § 2141.

The Present Invention Displays High Sensitivity

Applicants submit that the disclosure of Andersen does not encompass the entire scope and content of the present invention, because Andersen fails to teach all of the limitations of the present invention. Applicants note that the claims have been amended to recite the use of a "high sensitivity panel of peptides," a characteristic intrinsic to the panel of peptides. Support for this amendment can be found in the specification at, for example, pages 21-24. Applicants submit that Andersen does not teach or suggest any of the specific peptides recited in the present claims, much less that as a panel they would have enhanced sensitivity and be useful as a diagnostic method for tuberculosis. Furthermore, Applicants submit that at the time of filing, a person of ordinary skill in the art would not have been able to predict that the specific peptide panel of the present invention would have high sensitivity.

Applicants submit that Andersen fails to disclose that the set of eight to eleven peptides derived from ESAT-6 would display such enhanced activity. The peptide panel utilized in the present invention results in an assay with high sensitivity; the examples show that the presently claimed invention utilizing the recited peptide panels have a sensitivity of over 90%, compared to 69% for the tuberculin skin test (TST), a well established clinical diagnostic assay that employs PPD as the antigen. See the specification at, for example, page 22.

In addition, as previously noted, assays of the present invention, which utilize the recited peptide pools, are unexpectedly capable of eliciting a response in **both** CD4+ and CD8+ T cells. In contract, whole ESAT-6, disclosed in Andersen, only elicits a response in CD4+ T cells and not CD8+ T cells. See the specification at, for example, pages 24-25. This work was confirmed by the inventors in Chapman (*AIDS* 2002 Nov 22;16(17):2285-93). As pointed out by the Examiner, Andersen suggests the possibility of that "functionally equivalent to the polypeptide with respect to the ability of evoking a protective immune response (e.g. a DTH reaction)." Because Andersen discloses the use of whole ESAT-6, any such hypothetical peptides would only elicit responses in CD4+ T cells, and not CD8+ T cells. Importantly, it was not ***predictable*** that the panel of peptides disclosed and claimed in the present method, kit, and composition claims would have these properties.

Taken together, these features contribute to the high sensitivity of the presently claimed invention, and could not have been predicted at the time of filing. The 'state of the art' clinical diagnostic test at the time of filing (*i.e.*, the TST) demonstrated much lower sensitivity than the present invention.

The state of the art was also such that one could not predictably use a peptide-based assay in patient populations representing diverse ethnic groups. In contrast, the above-mentioned

features of the present invention provide the advantage of allowing the same pool of peptides to function with high sensitivity in assays with samples from a broad genetic range of infected individuals. See the specification at, for example, pages 21-22 and Table 2. At the time of filing, it was not known whether T cell epitopes in ESAT-6 (and thus, "functionally equivalent" sequences, which only elicited responses in CD4+ T cells) would be recognized by the T cell populations of a broad range of infected individuals. The present invention therefore provides a convenient method for diagnosing tuberculosis infection with a level of sensitivity greater in human population in general than could be predicted from the disclosure of Andersen. Accordingly, Applicants submit that Andersen fails to teach or suggest the sequence limitations of the present invention and does not encompass the entire scope and contents of the present invention. See *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-41 (2007) (clarifying that an improvement is not obvious if it is "more than the predictable use of prior art elements according to their established functions").

Objective Evidence of Nonobviousness

Applicants submit that the present invention is not obvious because (1) it demonstrates unexpected results and (2) the prior art teaches away from the present invention. See, *e.g.*, MPEP § 2141.01.

The high sensitivity demonstrated by the assays of the present invention, utilizing the recited peptide pools, demonstrate unexpected results. As previously noted, the peptide pools utilized in the present invention are capable of eliciting responses in both CD4+ T cells and CD8+ T cells. See the specification at, for example, pages 24-25. In contrast, Andersen utilizes ESAT-6 which is shown to only elicit a response in CD4+ T cells. *Id.* Thus, the peptide

pools utilized in the present invention provide greater sensitivity and specificity by eliciting responses from a diverse range of T cell populations, which could not have been predicted at the time of filing. Applicants further note that because the unexpected results are derived from disclosed and inherent qualities of the recited peptide pools, they need not be explicitly recited in the claims. See, *e.g.*, MPEP 2141.02(V).

In addition, the prior art teaches away from the present invention. In particular, Applicants note that animal experiments disclosed in Elhay *et al.*, Infection & Immunity, 1998, 66:3454-3456 ("Elhay") show that peptides derived from the C-terminal portion of ESAT-6 showed increased responses in animals relative to whole ESAT-6. See Elhay at, for example, page 3455. Based upon this prior art, a person of ordinary skill in the art would be motivated to select C-terminal peptides, as opposed to N-terminal peptides. Accordingly, Applicants submit that the prior art teaches away from the present invention.

Moreover, the peptide in the present invention (*i.e.*, ES15) corresponding to that in Elhay (*i.e.*, P8) was *not* the most reactive peptide in the panel. Indeed, the most reactive peptides in the present invention have sequences obtained from the N-terminus of the ESAT-6 protein, as opposed to the C-terminal peptides disclosed in Elhay. Thus, Elhay points in the wrong direction (C-terminal rather than N-terminal ESAT-6 peptides), away from the peptides with greater relative activity.

Based upon the foregoing arguments and secondary considerations of non-obviousness set forth above, Applicants submit that the present invention is not obvious, and respectfully request withdrawal of the rejection.

The Examiner Concedes Unobviousness

The Examiner concedes that "[t]he prior art of Andersen et al. does not specifically teach the individually claimed peptides as set forth in SEQ ID NO: 1-11." Even absent the compelling evidence of unobviousness described above, the mere fact that Andersen might suggest to a person of skill in the art that ESAT-6 contains antigenic peptides in no way makes obvious the peptides having the sequences of SEQ ID NOS: 1-8, much less the additional SEQ ID NOS: 9, 10 and/or 11. The Examiner must establish obviousness of the claimed subject matter, *i.e.*, the sequences with reasonable expectation of success. Here, the Examiner has made no showing, whether from a teaching, suggestion, or motivation or "common sense" to establish obviousness of the recited sequences. For this reason alone, the rejection is in error.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the invention described and defined by claims 88-109 are patentable over the rejections of the Examiner. Withdrawal of all rejections and allowance of the claims is requested.

Respectfully submitted,

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